SFDA SAFETY SIGNAL

"A signal is defined by the SFDA as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature"

17-8-2021

Saudi Food and Drug Authority (SFDA) – Safety Signal of Ivermectin and the Risk of Encephalopathy

The Saudi Food and Drug Authority (SFDA) recommends all health care professionals to be aware of the safety signal of ***Encephalopathy*** *associated with the use of* ***Ivermectin****. The signal has been originated as a result of routine pharmacovigilance monitoring activities.*

Introduction

Ivermectin is a semisynthetic, anthelmintic agent for oral or topical administration [1]. The drug binds selectively and with strong affinity glutamate-gated chloride ion channels causing hyperpolarization of the nerve or muscle cell, and death of the parasite [2]. Encephalopathy is a damage or disease that affects the brain characterized by confusion, memory loss, personality changes, trouble thinking clearly or focusing [3]. The aim of this review is to evaluate the risk of Encephalopathy associated with the use of Ivermectin and suggest regulatory recommendations if required.

Methodology

Signal Detection team at the National Pharmacovigilance Center (NPC) of Saudi Food and Drug Authority (SFDA) performed a comprehensive signal review using its national database as well as the World Health Organization (WHO) database (VigiBase), to retrieve related information for assessing the causality between Ivermectin and the risk of Encephalopathy [4]. We used the WHO- Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases [5].

Results

Case Review: The number of resulted cases for the combined drug/adverse drug reaction are 8 global Individual case safety reports (ICSRs) as of July 2021 [4]. The reviewers have selected and assessed the causality for top quality reported cases (2 ICSRs). All assessable ICSRs revealed possible association with one positive dechallenge [5].

Data Mining: The disproportionality of the observed and the expected reporting rate for drug/adverse drug reaction pair is estimated using information component (IC), a tool developed by WHO-UMC to

measure the reporting ratio. Positive IC reflects higher statistical association while negative values indicates less statistical association. The results of (IC= 0.6) revealed a positive statistical association for the drug/ADR combination, meaning "Encephalopathy" with the use of "Ivermectin" has been observed more than expected compared to other medications available in WHO database [4].

Literature Upon conducting a literature search, following cases of Encephalopathy associated with the use of Ivermectin were found.

A case report of a 13-year-old boy admitted to the hospital for impaired consciousness. Two hours before the onset of the neurologic symptoms, the boy received oral ivermectin at a dose 0.23 mg/kg. Ivermectin was prescribed to prevent scabies. Six hours following Ivermectin consumption, the neurologic symptoms have worsened and the boy suffered ataxia, binocular diplopia, pyramidal signs and vomiting, then fell in coma and sent to acute care area [6]. Another Ivermectin associated Encephalopathy was reported from Senegal. A 35-year-old male with no significant medical history was prescribed 150 mcg/kg oral Ivermectin. He experienced progressive deterioration of neurological symptoms until admission to hospital [7]. More interestingly, a broader pharmacovigilance review of all serious adverse events associated with Ivermectin was conducted. Total of 667 case reports of adverse events with Ivermectin were reviewed. Incidence of Encephalopathy was 8.2% [8].

Conclusion

The weighted cumulative evidence identified from the reported cases, literature and data minig are sufficient to support a causal association between Ivermectin and the risk of Encephalopathy. Health regulators and health care professionals must be aware of this potential risk and it is advisable to monitor any signs or symptoms in treated patients.

Report Adverse Drug Events (ADRs) to the SFDA

The SFDA urges both healthcare professionals and patients to continue reporting adverse drug reactions (ADRs) resulted from using any medications to the SFDA either online, by regular mail or by fax, using the following contact information:

National Pharmacovigilance Center (NPC)
Saudi Food and Drug Authority-Drug sector
4904 northern ring branch rd
Hittin District
Riyadh 13513 – 7148
Kingdom of Saudi Arabia
Toll free number: 19999
Email: NPC.Drug@sfda.gov.sa

References:

1. Merck Sharp & Dohme Corp. (2018). Summary of Product Characteristics (SPC) of Ivermectin Available at: https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=681888c9-af79-4b7d-ae80-c3f4f6f1effd [Accessed: 27 Jul 2021].
2. Lexicomp Online, Hudson, Ohio: UpToDate, Inc.; [Accessed: 27 Jul 2021].
3. Emedicine.medscape.com. 2021. Encephalopathy: Practice Essentials, Background, Clinical Manifestations. [online] Available at: https://emedicine.medscape.com/article/186101-overview> [Accessed 27 Jul 2021].
4. Uppsala Monitoring Center (UMC) (2020), Vigilyze database; Available at: https://vigilyze.who-umc.org [Accessed 27 Jul 2021].
5. Uppsala Monitoring Center (UMC) (2020), The use of the WHO-UMC system for standardized case causality assessment; Available at

6. dBaudou, E., Lespine, A., Durrieu, G., André, F., Gandia, P., Durand, C., & Cunat, S. (2020). Serious Ivermectin Toxicity and Human ABCB1 Nonsense Mutations. New England Journal of Medicine, 383(8), 787-789. doi:10.1056/nejmc1917344
7. Massi DG, Mansare ML, Traoré M, Ndiaye M, Diop AG, Ndiaye MM. Post-ivermectin encephalopathy in Senegal: a case report. Pan Afr Med J. 2017 Jul 18;27:202. doi: 10.11604/pamj.2017.27.202.12106. PMID: 28904727; PMCID: PMC5579453.
8. Campillo JT, Boussinesq M, Bertout S, Faillie JL, Chesnais CB. Serious adverse reactions associated with ivermectin: A systematic pharmacovigilance study in sub-Saharan Africa and in the rest of the World. PLoS Negl Trop Dis. 2021 Apr 20;15(4):e0009354. doi: 10.1371/journal.pntd.0009354. PMID: 33878105; PMCID: PMC8087035.